LABELING

Onyx® Liquid Embolic System

INSTRUCTIONS FOR USE

US05830178, US05785642, US05755658, US05695480, US05667767,
US05958444 and Other US and Foreign Patents Pending

It is important to read the instructions for use with careful attention to warnings prior to using this product.

Onyx and DMSO are sterile (dry heat) and non-pyrogenic

Syringes are sterile and non-pyrogenic

This device is intended for SINGLE USE ONLY. **DO NOT RESTERILIZE AND/OR REUSE.**

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

DESCRIPTION

Onyx® is a non-adhesive liquid embolic agent comprised of EVOH (ethylene vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide), and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. The Onyx Liquid Embolic System (LES™) consists of a 1.5 ml vial of Onyx, a 1.5 ml vial of DMSO, and three 1 ml Onyx delivery syringes. A DMSO compatible delivery micro catheter that is indicated for use in the neuro vasculature (e.g. Marathon™, Rebar™ or UltraFlow™ HPC catheters) is used to access the embolization site. Onyx is available in two product formulations, Onyx 18 (6% EVOH) and Onyx 34 (8% EVOH). Onyx 18 will travel more distally and penetrate deeper into the nidus due to its lower viscosity compared to Onyx 34. Final solidification occurs within five minutes for both product formulations.

PRINCIPLE OF OPERATION

Onyx is delivered by slow controlled injection through a micro catheter into the brain arteriovenous malformation under fluoroscopic control. The DMSO solvent dissipates into the blood, causing the EVOH copolymer and suspended tantalum to precipitate *in situ* into a spongy, coherent embolus. Onyx immediately forms a skin as the polymeric embolus solidifies from the outside to the inside, while traveling more distally in the lesion.

INDICATIONS FOR USE

Presurgical embolization of brain arteriovenous malformations (bAVMs).

CONTRAINDICATIONS

The use of the Onyx LES is contraindicated when any of the following conditions exist:

- When optimal catheter placement is not possible.
- When provocative testing indicates intolerance to the occlusion procedure.
- When vasospasm stops blood flow.

WARNINGS

- The safety and effectiveness of the Onyx LES as a long term implant has not been established.
- Not for use with premature infants (<1,500 g) or individuals with significant liver and kidney function impairment.
- Performing embolization to occlude blood vessels is a high risk procedure. This device should be used only by physicians with neurointerventional training and a thorough knowledge of the pathology to be treated, angiographic techniques, and super-selective embolization.
- AVM embolization may influence blood flow patterns, thereby subjecting arteries supplying the AVM or the brain proximal to the AVM to increased pressures. Increased arterial pressures could result in hemorrhagic complications
- Animal experimentation has shown that when Onyx escapes outside the vascular space, as might occur if the vessel wall is compromised, a subacute inflammatory response to the material may occur. Increased intracranial pressure due to unresorbed Onyx material in this space may cause tissue damage.
- Dimethyl sulfoxide (DMSO) can initiate the liberation of histamine and there has been an occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient being treated for interstitial cystitis. If anaphylactoid symptoms develop, appropriate therapy should be instituted.
- DMSO may interact with other embolic agents, such as polymer coated coils, e.g., gel coatings and suture material coated coils.
- Therapeutic embolization should not be performed when high blood flow precludes safe infusion of the embolic agent.
- **The microcatheter tip should be placed so that embolization of the bAVM occurs distal to any arterial vessels that may supply normal brain tissue or cranial nerves.**
- Failure to continuously mix Onyx for the required time may result in inadequate suspension of the tantalum, resulting in inadequate fluoroscopic visualization during delivery (see instructions for use). Inject Onyx immediately after mixing. If Onyx injection is delayed, tantalum settling can occur within the syringe resulting in poor visualization of Onyx during injection.
- Adequate fluoroscopic visualization must be maintained during Onyx delivery or non-target vessel embolization may result. If visualization is lost at any time during the embolization procedure, **HALT** Onyx delivery until adequate visualization is re-established.
- Premature solidification of Onyx may occur if micro catheter luer contacts any amount of saline, blood or contrast.
- Use only MTI micro catheters indicated for use in the neurovasculature, e.g., Marathon, Rebar and Ultraflow, and MTI syringes. Other micro catheters or syringes may not be compatible with DMSO and their use can result in thromboembolic events due to catheter degradation.
- Use only thumb pressure to inject the recommended rate of 0.16 mL/min. Do not exceed 0.3 ml/min injection rate. Animal studies have shown that rapid injection of DMSO into the vasculature may lead to vasospasm and/or angionecrosis. Using palm of hand to advance plunger may result in catheter rupture due to overpressurization in the event of catheter occlusion.
- Do not allow more than 1 cm of Onyx to reflux back over catheter tip. Excessive Onyx reflux may result in difficult catheter removal.
- After using a micro catheter with Onyx, do not attempt to clear or inject any material through it. Such attempts may lead to embolus or embolization of an unintended area.

- STOP injection if Onyx is not visualized exiting catheter tip. If the catheter becomes occluded, over-pressurization can occur. During Onyx injection, continuously verify that Onyx is exiting the catheter tip. Testing has shown that over-pressurization and rupture can occur if only a volume of 0.05 ml of Onyx is injected and is not visualized exiting the catheter tip.
- STOP injection if increased resistance to Onyx injection is observed. If increased resistance occurs, determine the cause (e.g., Onyx occlusion in catheter lumen) and replace the catheter. Do not attempt to clear or overcome resistance by applying increased injection pressure, as use of excessive pressure may result in catheter rupture and embolization of unintended areas.
- DO NOT interrupt Onyx injection for longer than two minutes prior to re-injection. Solidification of Onyx may occur at the catheter tip resulting in catheter occlusion, and use of excessive pressure to clear the catheter may result in catheter rupture.

PRECAUTIONS

- The safety and effectiveness has not been studied in the following patient populations:
    - Pregnant and nursing women
    - Individuals less than 18 years old
    - Individuals with aneurysms not associated with a bAVM nidus, or distal feeders to a bAVM nidus or dural AV fistulas
- Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.
- A garlic-like taste may be noted by the patient with use of Onyx due to the DMSO component. This taste may last several hours. An odor on the breath and skin may be present.
- Inspect product packaging prior to use. Do not use if sterile barrier is open or damaged.
- Use prior to expiration date.
- Verify that the catheters and accessories (see directions for use) used in direct contact with the Onyx polymer are clean and compatible with the material and do not trigger polymerization or degrade with contact. Use only MTI micro catheters indicated for use in the neurovasculature, e.g., Marathon, Rebar and Ultraflow, and MTI syringes. Other micro catheters or syringes may not be compatible with DMSO and their use can result in thromboembolic events due to catheter degradation. Refer to the Warnings and Directions for Use sections.
- Wait a few seconds following completion of Onyx injection before attempting catheter retrieval. Failure to wait a few seconds to retrieve the micro catheter after Onyx injection may result in fragmentation of Onyx into non-target vessels.

Difficult catheter removal or catheter entrapment may be caused by any of the following:

- Angioarchitecture: very distal bAVM fed by afferent, lengthened, and tortuous pedicles
- Vasospasm
- Reflux

Should catheter removal become difficult, the following will assist in catheter retrieval:

- Carefully pull the catheter to assess any resistance to removal.
- If resistance is felt, remove any "slack" in the catheter.
- Gently apply traction to the catheter (approximately 3-4 cm of stretch to the catheter).
- Hold this traction for a few seconds and release. Assess traction on vasculature to minimize risk of hemorrhage.
- This process can be repeated intermittently until catheter is retrieved.

Alternate Technique for Difficult to Remove Catheters.

- Remove all slack from the catheter by putting a few centimeters of traction on the catheter to create a slight tension in the catheter system.
- Firmly hold the catheter and then pull it using a quick wrist snap motion (from left to right) 10 – 15 centimeters to remove the catheter from the Onyx cast.
- Note: Do not apply more than 20 cm of traction to catheter, to minimize risk of catheter separation.

For entrapped catheters:

- Under some difficult clinical situations, rather than risk rupturing the malformation and consequent hemorrhagic complications by applying too much traction on an entrapped catheter, it may be safer to leave the micro catheter in the vascular system.
- This is accomplished by stretching the catheter and cutting the shaft near the entry point of vascular access allowing the catheter to remain in the artery.
- If the catheter breaks during removal, distal migration or coiling of the catheter may occur. Same day surgical resection should be considered to minimize the risk of thrombosis.

TRAINING

Serious, including fatal, consequences could result with the use of the Onyx LES without adequate training. Contact your Micro Therapeutics Inc. sales representative for information on training courses

ADVERSE EVENTS

Potential Adverse Effects of the Device on Health

A prospective, randomized, multi-center clinical trial compared Onyx LES to the TRUFILL n-Butyl cyanoacrylate (TRUFILL) liquid embolic system for the presurgical treatment of bAVMs. The primary endpoint of the study required 100 patients to be evaluated for effectiveness. An additional 17 patients were enrolled under a continued access provision. Safety was evaluated for all 117 patients in the Intention to Treat (ITT) cohort, which includes all patients in which treatment of the assigned device was attempted. Safety was assessed based on the nature and severity of adverse events.

The safety profile for the two groups was comparable. Many of the events occurred during, or post surgery, as opposed to during, or post embolization, with the embolization agents.

Two patients died during the course of the clinical trial. Both deaths occurred in the Onyx group and both occurred following surgical resection. A third death occurred after the patient had been discharged to a rehabilitation center for persistent neurological deficits, but the patient had completed study follow-up.

The table below provides a summary of the adverse events that occurred during the study.

Table 1: Incidence of Complications

Incidence of Complications				
EVENT NAME	TRUFILL N=63		Onyx N=54	
	# of events	# of patients (%)	# of events	# of patients (%)
Death	0	0 (0.0%)	3	3 (5.6%)
Headache +/- nausea and vomiting	84	47 (74.6%)	74	45 (83.3%)
Patient discomfort	48	37 (58.7%)	58	39 (72.2%)
Laboratory/Imaging abnormalities	58	40 (63.5%)[+]	53	39 (72.2%)[+]
Endocrine/Metabolic	31	27 (42.9%)	29	26 (48.2%)
Hematologic	14	13 (20.6%)	13	12 (22.2%)
Asymptomatic MRI/CT Findings	6	6 (9.5%)	5	4 (7.4%)
Respiratory/Pulmonary	2	2 (3.2%)	3	3 (5.6%)
General	3	3 (4.8%)	2	2 (3.7%)
Gastrointestinal (GI)	0	0 (0%)	1	1 (1.9%)
Cardiac	1	1 (1.6%)	0	0 (0%)
Infectious/Inflammatory	1	1 (1.6%)	0	0 (0%)
Worsening Neurologic Status	40	28 (44.4%)[+]	43	35 (64.8%)[+]
Persistent	23	15 (23.8%)	22	16 (29.6%)
Resolved	17	14 (22.2%)	21	19 (35.2%)
Hyperglycemia	53	45 (71.4%)	39	35 (64.8%)
Infection	15	14 (22.2%)	16	14 (25.9%)
Bleeding and/or Low Hct requiring transfusion	17	17 (27.0%)[+]	15	14 (25.9%)[+]
Surgical Bleeding	9	9 (14.3%)	12	11 (20.4%)
Decreased Hct Requiring Transfusion	5	5 (7.9%)	3	3 (5.6%)
GI Bleeding	2	2 (3.2%)	0	0 (0%)
Other – bAVM Rupture	1	1 (1.6%)	0	0 (0%)
Intracranial Hemorrhage	13	11 (17.5%)	13	13 (24.1%)
Medication reaction	5	5 (7.9%)	11	10 (18.5%)
*Failed access**	13	12 (19.0%)	9	8 (14.8%)
Access site bleeding	3	3 (4.8%)	7	4 (7.4%)
Fever	4	4 (6.3%)	7	7 (13.0%)
*Delivery Catheter removal difficulty**	1	1 (1.6%)	6	5 (9.3%)
*Poor penetration/visualization**	0	0 (0%)	6	5 (9.3%)
Hypotension	0	0 (0%)	5	3 (5.6%)
Stroke	2	2 (3.2%)	4	4 (7.4%)
Cardiac arrhythmia	2	2 (3.2%)	2	2 (3.7%)
Hydrocephalus	1	1 (1.6%)	2	2 (3.7%)
SIADH (Syndrome of inappropriate antidiuretic hormone secretion, dilutional hyponatremia)	0	0 (0%)	2	2 (3.7%)
Vessel Dissection	0	0 (0%)	2	2 (3.7%)
Hypertension	3	3 (4.8%)	1	1 (1.9%)
Limb ischemia	2	1 (1.6%)	1	1 (1.9%)

Incidence of Complications				
EVENT NAME	TRUFILL N=63		Onyx N=54	
Respiratory failure	4	4 (6.3%)	1	1 (1.9%)
Seizures	5	4 (6.3%)	1	1 (1.9%)
UTI (Urinary tract infection)	1	1 (1.6%)	1	1 (1.9%)
Vasospasm	5	4 (6.3%)	1	1 (1.9%)
Vaso-vagal episode	1	1 (1.6%)	1	1 (1.9%)
Cardiac arrhythmia/hypertension	2	2 (3.2%)	0	0 (0%)
*Embolization of unintended vessel**	7	6 (9.5%)	0	0 (0%)
*Premature polymerization time**	3	3 (4.8%)	0	0 (0%)
Vascular access complication	2	2 (3.2%)	0	0 (0%)
*Prolonged polymerization time**	5	5 (7.9%)	0	0 (0%)

[+] Patients could be counted multiple times within categories so the sum of percentages within the subcategories may not equal the total for the main category

*Technical or Procedural Event only with no clinical sequelae.

The following events occurred in one patient each in the Onyx group and did not occur in the TRUFILL group: catheter shaft rupture, delivery catheter rupture, fragmentation of Onyx, hypoxia, laryngospasm, peptic ulcer disease, psychotic episode, pulmonary edema, skin abrasion, subintimal injection, tachypnea, and tongue swelling. The following events occurred in one patient each in the TRUFILL group, and did not occur in the Onyx group: catabolic state, coagulopathy, corneal abrasion, elective carotid aneurysm surgery, high flow fistula, multi-organ system complications, myopathy/neuropathy, orthostasis, post craniotomy revision, surgical revision, transient ischemic attack (TIA), trauma, ureteral perforation, and vocal cord paralysis.

Additional adverse events, which may be associated with embolization procedures include:

- Allergic reaction
- Thrombocytopenia
- Pulmonary embolism

CLINICAL STUDY RESULTS

Study Purpose

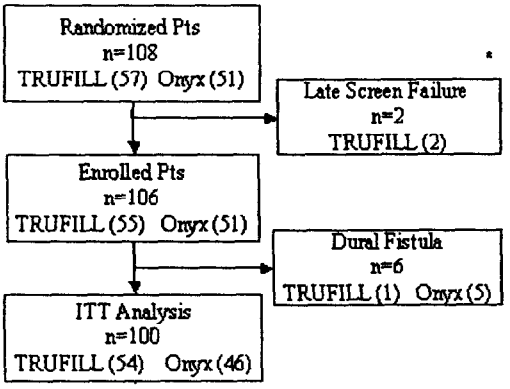
The purpose of this study was to assess the safety and effectiveness of Onyx LES in the presurgical embolization of bAVMs. Device safety was assessed by comparing the incidence of adverse events. The primary efficacy endpoint was the angiographic reduction in bAVM size (volume) achieved. A level of 50% or greater reduction in size was established as a criterion for success. The objective was to demonstrate that Onyx is no worse than TRUFILL, a legally marketed bAVM embolization device, in terms of effectiveness within a specified clinical tolerance (20%).

Design

This study was designed as a prospective, randomized, multi-center clinical comparison of the MTI Onyx LES to the Cordis TRUFILL n-Butyl cyanoacrylate (TRUFILL) liquid embolic agent for the presurgical treatment of bAVMs. The primary endpoint of the study required 100 patients to be evaluated for effectiveness. One hundred and eight patients were randomized: two of these patients were late screen

failures, having been deemed anatomically unsuitable for embolization by the treating physician. Thus, 106 patients were enrolled and randomized, on a 1:1 basis, at 20 clinical sites in the U.S. to either embolization with Onyx or TRUFILL resulting in 51 patients in the Onyx group and 55 patients in the TRUFILL group. Six patients were deemed by the core lab to be dural fistulae subjects, and thus were excluded from the efficacy analysis, resulting in 100 patients evaluated for efficacy. Demographic information, including bAVM characteristics, is presented on 102 patients, which includes information on the 2 patients who were late screen failures. A summary of patient enrollment is provided in Figure 1, below.

Figure 1: Efficacy Endpoint Patient Flow



*Late screen failures: anatomically unsuitable for embolization

An additional 17 patients were enrolled under a continued access provision. Safety was evaluated for all 117 patients in the Intention to Treat (ITT) cohort, which includes all patients in which treatment of the assigned device was attempted. Safety was assessed based on the nature and severity of adverse events, and is reported in Table 1.

All patients with a bAVM in the cerebral cortex, cerebellum or dura mater of a Spetzler-Martin grade I-IV were randomized to either the Onyx or TRUFILL treatment arms. For patients randomized to Onyx, the formulation used (Onyx 18 alone, Onyx 34 alone, or combination of Onyx 18 and 34) was at the physician's discretion. For patients randomized to TRUFILL, the oil:TRUFILL ratio used was also at the physician's discretion. Patients underwent embolization procedure(s) to reduce the size of the bAVM prior to surgical resection. Neurological assessments (i.e., NIH scale, Barthel Index, and Glasgow Index) were performed prior to and post embolization and/or surgical resection, when surgery was performed. Although patients were to undergo total surgical resection as an enrollment criterion, 6 patients in the TRUFILL group and 5 patients in the Onyx group did not undergo total resection.

Methods

Patients were evaluated for potential enrollment based on the inclusion and exclusion criteria of the protocol, as described below:

Inclusion Criteria:

- The patient has a bAVM in the cerebral cortex, cerebellum or dura mater.
- The bAVM has a Spetzler-Martin grade of I – IV.
- The patient is a candidate for surgical resection of the bAVM post embolization.

- The patient is clinically and neurologically stable for a minimum of 24 hours prior to the embolization procedure.
- The patient can be of any age.

Exclusion Criteria

- The patient has a bAVM with a high flow AV fistula that the investigator has determined to be unsuitable for embolization.
- The bAVM has a Spetzler-Martin grade of V.
- The patient is participating in another research study involving another investigational device, procedure or drug.
- The bAVM has been previously embolized with another agent.

Review of patient demographics and baseline bAVM characteristics show no differences between the Onyx and TRUFILL groups. bAVM size was found to be slightly higher in the Onyx group, however this difference was not statistically significant. Both groups had the majority of patients treated with bAVMs having a Spetzler-Martin grade of either II or III. All other bAVM characteristics were comparable between the two groups. Patient demographics and bAVM characteristics are presented in the tables, below.

Table 2: Patient Demographics

	Group	
Patient Demographics	**TRUFILL (n=56)**	**Onyx (n=46)**
Age (yrs):		
Mean+/-SD (N)	35.1 ± 14.3 (56)	40.3 ± 16.3 (46)
Median (Range):	36.0 (10.0 – 66.0)	42.5 (7.0 – 72.0)
Gender:		
Male	48.2% (27/56)	43.5% (20/46)
Female	51.7% (29/56)	56.5% (26/46)

Demographics include 2 late screen failure patients

Table 3: bAVM Characteristics*

(n=103 bAVMs in n=102 pts) Pretreatment Assessment		TRUFILL (n=57 bAVMs in 56 patients)		Onyx (n=46 bAVMs in 46 patients)	
bAVM Location	*Right*	55.4%	(31/56)	63.0 %	(29/46)
	Left	41.1%	(23/56)	34.8 %	(16/46)
	Midline	3.6 %	(2/56)	2.2 %	(1/46)
bAVM Located in eloquent area of Brain		48.2%	(27/56)	45.7 %	(21/46)
Venous Drainage	*Deep*	8.9 %	(5/56)	15.2 %	(7/46)
	Superficial	62.5%	(35/56)	63.0 %	(29/46)
	Both	28.6%	(16/56)	21.7 %	(10/46)
Spetzler-Martin Grade	*I*	25.0%	(14/56)	10.9 %	(5/46)
	II	25.0 %	(14/56)	43.5%	(20/46)
	III	30.4%	(17/56)	26.1 %	(12/46)
	IV	19.6%	(11/56)	19.6 %	(9/46)
bAVM Size (Core Lab, mm^3)	*Mean+/- SD*	16.0+/- 20.0		26.3+/- 45.2	
	Median	8.1		13.6	
	Range	0.08-94.9		0.17-290.5	

*bAVM Characteristics include 2 late screen failure patients

Upon enrollment, a baseline clinical neurological examination was performed and grading scales including Barthel Index, Glasgow Coma Scale (GCS) and NIH Stroke Scale (NIHSS) were recorded. In addition, baseline CT, MRI, and/or angiograms were performed for complete characterization of the bAVM prior to randomization. Following randomization, patients were embolized as deemed appropriate by the investigator. The physician determined the number of embolization stages and the percent bAVM reduction based on factors specific to each patient, such as bAVM size, number of feeders, fistulous connections, and location relative to eloquent territory. The majority of patients in each group underwent one embolization procedure. The number of embolization procedures ranged from one to seven, as summarized in the table below. In the Onyx group 33 patients were treated with the Onyx 18 formula, 2 patients were treated with the Onyx 34 formula and 11 patients were treated with both formulations.

Coils were used as adjunctive therapy in 23 of 91 TRUFILL procedures and 8 of 82 Onyx procedures. One Onyx patient received a single embolization treatment with Onyx; the second embolization attempt was a failure for Onyx delivery, and the patient was crossed over to treatment with TRUFILL. Two patients in the TRUFILL group received PVA.

Table 4: Embolization Procedures Per Patient

# of Embolization Procedures	TRUFILL (n=54)		Onyx (n=46)	
	# of Pts	**% of Pts**	**# of Pts**	**% of Pts**
1	34	63.0%	26	56.5%
2	9	16.7%	11	23.9%
3	7	13.0%	6	13.0%
4	2	3.7%	1	2.2%
5	2	3.7%	1	2.2%
6	0	0.0%	0	0.0%
7	0	0.0%	1	2.2%
Total # Pts	54	100%	46	100%
Total Procedures	91		82	
Avg # Procs per Pt (min - max)	1.7 (1 - 5)		1.8 (1 - 7)	
Number of days between patient's first and last embolization procedure	**Range: 1 – 197 days**		**Range: 2 – 408 days**	

After each embolization procedure, patients were neurologically evaluated using the same scales as pre-procedure Upon completion of the embolization phase, patients were referred for surgery. If, in the physician's opinion, surgical treatment was not an option, other nonsurgical courses of treatment including radiosurgery or no further treatment were implemented. Patients that were completely resected received a final neurological examination with grading scale assessments as a final evaluation of the protocol. Those patients with bAVMs that were not completely resected underwent follow-up evaluations at 3 and 12 months. The follow-up assessments included a complete neurological examination with grading scales including Barthel Index, Glasgow Outcome Score (GOS) and NIH Stroke Scale (NIHSS) and evaluation of safety.

Eleven patients were not completely resected and will be followed for 3 years. Of these 11 patients, 5 patients were treated with Onyx and 6 were treated with TRUFILL. Six patients, 1 Onyx and 5 TRUFILL underwent radiosurgery. Two Onyx patients had partial resections and radiosurgery. One TRUFILL patient had only partial resection. Two Onyx patients had no further treatment following embolizations.

Effectiveness Endpoints

The primary effectiveness measure was technical success as measured by angiographic reduction in bAVM size (volume) of 50% or greater as assessed by core laboratory. Angiographic size reduction is defined as the change from the original bAVM size prior to any embolization procedure, to the bAVM size after the patient's final embolization procedure.

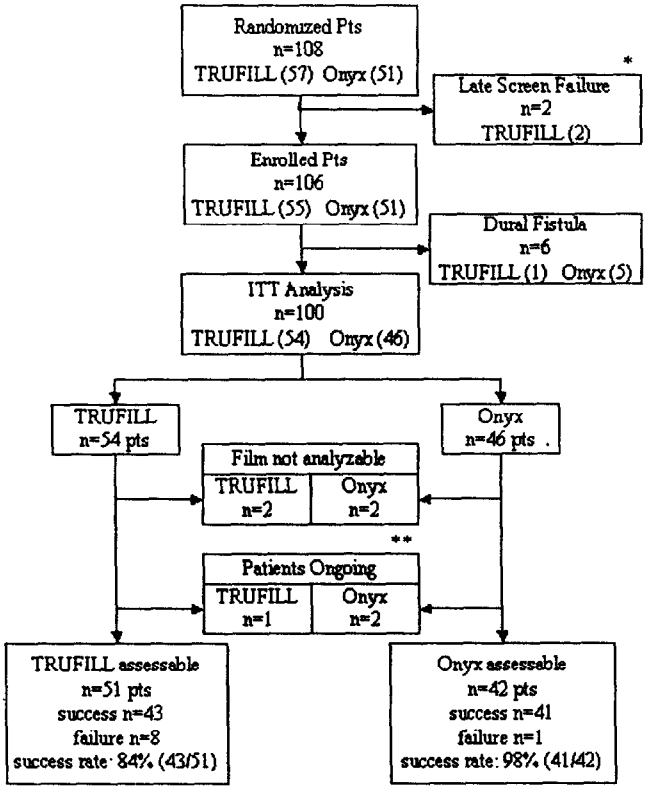
The results for the primary effectiveness endpoint demonstrate that the two products are comparable with regard to bAVM occlusion efficacy, and thus, the primary study hypothesis (i.e., Onyx is no worse than TRUFILL in terms of bAVM obliteration defined as $\geq$ 50% occlusion as assessed by core angiographic laboratory) was achieved using an Intention to Treat analysis (ITT) approach (Table 5).

An analysis for the primary effectiveness endpoint was performed with all those patients in the Intent-to-Treat (ITT) population in which the core lab was able to make as assessment of the degree of bAVM

occlusion. Each patient was analyzed based on their treatment assignment regardless of course of treatment and evaluated after the final stage of embolization prior to surgical intervention.

A summary of the Intention-to-Treat analysis of patient flow with results is provided in Figure 2, below:

Figure 2: ITT Analysis Flowchart



*Late screen failures: anatomically unsuitable for embolization
**Patients ongoing: continuing embolization at time of data closure

Primary endpoint analysis demonstrates non-inferiority of the Onyx device to TRUFILL. The Primary Endpoint analysis is presented in Table 5, below.

Table 5: Primary Endpoint Summary

Core Lab Angiographic Success	TRUFILL (n= 54)	Onyx (n= 46)	Difference [95% CI]	Relative Risk [95% CI]
Intent-to-Treat Analysis	84.3% (43/51)	97.6% (41/42)	13.3% [2.3%, 24.3%,]	1.16 [1.01,1.32]

Diff = Onyx – n-BCA; SE = sqrt($p_1q_1/n_1+p_2q_2/n_2$); CI = Diff±1.96*SE
RR = Onyx/n-BCA; SE = sqrt{$(1- p_1)/ n_{11}+(1- p_2)/ n_{21}$}; CI = RR*exp(±1 96*SE)

The study had two secondary effectiveness endpoints: surgical blood loss and surgical resection time. There was considerable variability in these endpoints primarily due to the complexity of this disease state and the associated surgery for resection. No statistically significant differences were observed for either of these two secondary endpoints.

Table 6: Secondary Effectiveness Endpoint Summary

Secondary Endpoints	TRUFILL* (n= 54)	Onyx* (n= 46)
Blood loss index		
mean±sd (n)	892 ± 1067 (44)	1127 ± 1401 (43)
Median	475	550
range (min, max)	100-5000	50-6550
Surgical resection time		
mean±sd (n)	411 ± 201 (42)	399 ± 179 (42)
Median	344	366
range (min, max)	150, 1019	82, 940

* A total of 89 patients had surgical resection of their bAVM (either total or partial), 46 patients in the n-BCA group and 43 patients in the Onyx group. Data on blood loss was available for 44 patients in the n-BCA group and 43 patients in the Onyx group. Data on surgical resection time was available for 42 patients in the n-BCA group and 42 patients in the Onyx group .

Safety Endpoints

Safety was assessed by the nature and severity of adverse events. The adverse events are shown in Table 1.

Deaths

There were 3 deaths reported in patients treated with Onyx: two patients died during the clinical study period and 1 patient died after study follow-up was completed. In all cases, patients underwent surgical resection following embolization. The first patient developed intra- and peri-operative bleeding which resulted in a hematoma and infarction. The patient expired following withdrawal of care. The second patient had a large post-surgical middle cerebral artery (MCA) infarction and expired following withdrawal of care. The third patient who died following study follow-up completion sustained a significant neurological deficit after a surgery-related hemorrhage and required long term skilled nursing home care. The patient died several months after discharge in the nursing home.

The possible role of Onyx in the patient deaths, if any, is unknown.

The technical/procedural events encountered during embolization were similar for the two groups except for delivery catheter removal difficulty, which occurred six (6) times in five (5) patients in the Onyx group and in only one (1) patient in the TRUFILL group. All catheters in the Onyx group were able to be removed. The catheter in the TRUFILL group remained in the patient. Table 7, below, summarizes the technical/procedural events related to the respective embolic agents:

Table 7: Technical/Procedural Events – Embolic Agent*

EVENT NAME	TRUFILL N=63		Onyx N=54	
Delivery Catheter removal difficulty	1	1 (1.6%)	6	5 (9.3%)
Poor penetration/visualization	0	0 (0%)	6	5 (9.3%)
Poor visualization of Onyx	0	0 (0%)	1	1 (1.9%)
Embolization of unintended vessel	7	6 (9.5%)	0	0 (0%)
Premature polymerization time	3	3 (4.8%)	0	0 (0%)
Prolonged polymerization time	5	5 (7.9%)	0	0 (0%)

*Includes 17 continued access patients

Clinical Study Conclusions

In conclusion, the clinical study has met its study hypothesis, demonstrating non inferiority of Onyx in comparison to TRUFILL in the ability to occlude a bAVM prior to surgical resection. Secondary efficacy endpoint analysis shows no difference in surgical blood loss and surgical resection time between the two groups. The safety profile has been shown to be similar between the two groups.

HOW SUPPLIED

Onyx is available in two product formulations, Onyx 18 (6% EVOH) and Onyx 34 (8% EVOH).

- Onyx 18 (nominal viscosity of 18 cSt at 40°C): Recommended when feeding pedicle injections will be conducted close to the nidus.
- Onyx 34 (nominal viscosity of 33 cSt at 40°C): Recommended for embolizing higher flow and larger fistulous components.

Onyx 18 will travel more distally and penetrate deeper into the nidus due to its lower viscosity compared to Onyx 34. Final solidification occurs within five minutes for both product formulations.

STORAGE

Store Onyx and DMSO between -20° and 55°C. Prior to use, maintain product temperature between 19° and 24°C. If product freezes due to exposure to colder temperatures, thaw at room temperature before use.

DIRECTIONS FOR USE

WARNING: Verify that adequate sedation is used throughout the embolization procedure. Insufficient sedation may result in patient discomfort or movement. Patient movement during embolic agent injection may result in embolization of an unintended vessel.

NOTE: Adjunctive coil use should be considered if angiography shows that venous drainage of the bAVM appears almost simultaneously with arterial opacification. Based on results from in vitro and in vivo testing, coil placement prior to Onyx injection should be considered for feeding pedicles with AV fistulae having flow rates exceeding 200 ml/min and vessel diameters of 3 mm or greater.

1. Shake Onyx at least 20 minutes on an Onyx mixer[1] at a setting of 8. Continue mixing until ready to inject Onyx per step 5.

   WARNING: Failure to continuously mix Onyx for the required time may result in inadequate suspension of the tantalum, resulting in inadequate fluoroscopic visualization during delivery.

2. Confirm micro catheter placement with injection of contrast agent per institutional procedure.

   WARNING: Use only MTI micro catheters indicated for use in the neurovasculature, e.g., Marathon, Rebar and Ultraflow, and MTI syringes. Other micro catheters or syringes may not be compatible with DMSO and their use can result in thromboembolic events due to catheter degradation.

3. Flush contrast from micro catheter with 10 ml of saline. Leave the syringe connected.
4. Filling catheter deadspace: aspirate approximately 0.8 ml of MTI DMSO into the yellow MTI 1 ml DMSO syringe. Inject DMSO into delivery micro catheter in sufficient volume to fill catheter deadspace. Refer to delivery catheter labeling for deadspace volume.

   WARNING: Use only the MTI 1 ml syringe to inject DMSO and Onyx. Other syringes may not be compatible with DMSO.

5. Ensure that Onyx has been mixed per step 1. Fill white MTI 1 ml syringe with Onyx through an 18 or 20 gauge needle. As soon as the DMSO has been injected into the catheter deadspace, remove the DMSO syringe, hold the catheter hub in a vertical position, and overfill and wash the luer hub with the balance of the DMSO.
6. ***Immediately*** connect the Onyx syringe to the hub, making sure there is no air in the hub during the connection. For optimal fluoroscopic visualization, quickly point the syringe vertically to create an interface between the DMSO and the Onyx.

   WARNING: Premature solidification of Onyx may occur if micro catheter luer contacts saline, blood or contrast of any amount.

7. While holding the syringe vertically, begin injecting Onyx to displace DMSO. Based on clinical practice, it is recommended that Onyx be injected at a slow, steady rate of 0.16 ml/min (0.25 ml/90 sec). Do not exceed 0.3 ml/min.

   WARNINGS: Inject Onyx immediately after mixing. If Onyx injection is delayed, tantalum settling can occur within the syringe resulting in poor visualization of Onyx during injection.

   Do not exceed 0.3 ml/min injection rate. Animal studies have shown that rapid injection of DMSO into the vasculature may lead to vasospasm and/or angionecrosis.

   Only use thumb pressure to inject Onyx. Using palm of hand to advance plunger may result in catheter rupture due to overpressurization in the event of catheter occlusion.

   Adequate fluoroscopic visualization must be maintained during Onyx delivery or non-target vessel embolization may result. If visualization is lost at any time during the embolization procedure, **HALT** Onyx delivery until adequate visualization is re-established.

8. Continue holding syringe vertically until Onyx passes through the catheter hub. Once Onyx passes through the hub, hold syringe in a more comfortable position and continue injecting Onyx at the slow, steady, recommended rate of 0.16 ml/min. Monitor volume injected to correspond to volume of vascular space being filled.

   WARNINGS: Do not allow more than 1 cm of Onyx to reflux back over catheter tip. Excessive Onyx reflux may result in difficult catheter removal.

   After using a micro catheter with Onyx, do not attempt to clear or inject any material through it. Such attempts may lead to embolus or embolization of an unintended area.

   - STOP injection if Onyx is not visualized exiting catheter tip. If the catheter becomes occluded, over-pressurization can occur. During Onyx injection, continuously verify that

[1]Scientific Industries Genie 2, Model No 120V SI-0240, Vial Attachment No OA- 0570-010

Onyx is exiting the catheter tip. Testing has shown that over-pressurization and rupture can occur if 0.05 ml of Onyx is injected and is not visualized exiting the catheter tip.

- STOP injection if increased resistance to Onyx injection is observed. If increased resistance occurs, determine the cause (e.g., Onyx occlusion in catheter lumen) and replace the catheter. Do not attempt to clear or overcome resistance by applying increased injection pressure, as use of excessive pressure may result in catheter rupture and embolization of unintended areas.
- DO NOT interrupt Onyx injection for longer than two minutes prior to re-injection. Solidification of Onyx may occur at the catheter tip resulting in catheter occlusion, and use of excessive pressure to clear the catheter may result in catheter rupture.

9. Upon completion of Onyx injection, wait a few seconds, slightly aspirate syringe, and then gently pull the catheter to separate it from the Onyx cast.

Difficult catheter removal or catheter entrapment may be caused by any of the following:

- Angioarchitecture: very distal bAVM fed by afferent, lengthened, and tortuous pedicles
- Vasospasm
- Reflux

Should catheter removal become difficult, the following will assist in catheter retrieval:

- Carefully pull the catheter to assess any resistance to removal.
- If resistance is felt, remove any "slack" in the catheter.
- Gently apply traction to the catheter (approximately 3-4 cm of stretch to the catheter).
- Hold this traction for a few seconds and release. Assess traction on vasculature to minimize risk of hemorrhage.
- This process can be repeated intermittently until catheter is retrieved.

Alternate Technique for Difficult to Remove Catheters.

- Remove all slack from the catheter by putting a few centimeters of traction on the catheter to create a slight tension in the catheter system.
- Firmly hold the catheter and then pull it using a quick wrist snap motion (from left to right) 10 – 15 centimeters to remove the catheter from the Onyx cast.
- Note: Do not apply more than 20 cm of traction to catheter, to minimize risk of catheter separation.

For entrapped catheters:

- Under some difficult clinical situations, rather than risk rupturing the malformation and consequent hemorrhagic complications by applying too much traction on an entrapped catheter, it may be safer to leave the micro catheter in the vascular system.
- This is accomplished by stretching the catheter and cutting the shaft near the entry point of vascular access allowing the catheter to remain in the artery.
- If the catheter breaks during removal, distal migration or coiling of the catheter may occur. Same day surgical resection should be considered to minimize the risk of thrombosis.

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